REMARKS/ARGUMENTS

The final Office Action of December 7, 2009, has been carefully considered and these amendments and remarks are responsive thereto. Claims 1, 7, 10, 11, 14-18, 23 and 31 are pending and claims 29 and 30 have been withdrawn.

Election/Restrictions and Rejoinder Practice

Withdrawn claim 29 has been amended to so that it is directed to a process that has all of the features of product claim 1, as amended. Specifically, claim 29 has been amended to include the amendment to product claim 1, i.e., "wherein at least 63% of the metaxalone has a particle size more than 1.8μm in diameter." Support for the amendments to claim 1 and 29 can be found in Table 3, on page 7 of the specification as originally filed. It is respectfully submitted that claim 29 be rejoined with claim 1. Claims 30 and 31 are directed to a process or composition wherein the metaxalone has a specific surface area per unit volume of more than $2.5m^2/cm^3$, and withdrawn method claim 30 is directed to a process that has all of the features of product claim 31, as amended, i.e., "wherein at least 63% of the metaxalone has a particle size more than 1.8μm in diameter." As noted above, support for this amendment can be found in Table 3, on page 7 of the specification as originally filed. It is respectfully submitted that claim 30 be rejoined with claim 31. The Office Action mailed December 7, 2009, did not comment on claims 29 and 30, or rejoinder thereof.

Rejections under 35 USC 103

Claims 1, 7, 10, 11, 14-18, 23 and 31 were rejected under 35 U.S.C 103(a) as being unpatentable over Liversidge et al. (U.S. Patent 5,145,684) in view of Scaife et al. (U.S. Patent 6,407,128). Claims 1, 7, 10, 11, 14-18, 23 and 31 were rejected under 35 U.S.C 103(a) as being unpatentable over Martin et al. (U.S. Patent 4,344,934) in view of Scaife et al. (U.S. Patent 6,407,128). The Applicants respectfully disagree and traverse the rejections. Applicants incorporate herein by reference the Response filed June 3, 2009 (incorrectly identified by the

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Office in the Office Action being filed July 13, 2009) and October 27, 2008 in connection with the arguments for nonobviousness over the cited art.

The cited references, alone or in combination, do not teach the claimed features of claim 1 as amended. Neither of the primary references, Liversidge and Martin, teaches the claim feature of a "pharmaceutical composition comprising metaxalone." Neither primary reference teaches or suggests the claim feature of a pharmaceutical composition comprising metaxalone "in a micronized form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when orally administered to a patient on an empty stomach." Neither primary reference teaches or suggests the claim feature "wherein at least 99% of the metaxalone has a particle size not more than 10μm in diameter and wherein at least 63% of the metaxalone has a particle size more than 1.8μm in diameter."

Rather, Liversidge teaches that "[m]any factors **can** affect bioavailability including dosage form and various properties" and that "[p]oor bioavailability is a significant problem encountered in the development of pharmaceutical compositions." Liversidge, col. 1, lines 12-19. Liversidge discloses a method of increasing solubility of hydrophobic drugs by formulating them in nanoparticulate (at least 90 percent of particles of 400 nm diameter or less; see Liversidge col. 5, lines 20-40) crystalline form. In one of the comparative examples (Example 14, Bioavailability testing, column 13, lines 55-67 and column 14, lines 1-4), Liversidge compares the bioavailability of Steroid A achieved by a nanoparticulate dispersion composition against an unmilled material of size range 100 μm. Liversidge reported a greater bioavailability (of 14.8 ± 3.5%) for the nanoparticulate composition of than for the unmilled material (2.1 ± 1.0 %). **Thus, according to Liversidge, a microparticle, in the range of 100μm, resulted in poor bioavailability.** Based on Liversidge, one of ordinary skill in the art would at most conclude that to increase the bioavailability of Steroid A, one would have to reduce the size of the Steroid A from a microparticle size to a nanoparticle size of 400 nm diameter or less. Indeed, Liversidge

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teaches away from using microparticle sized drugs in favor of nanoparticle sized drugs of 400 nm diameter or less to improve bioavailability.

The proposed combination of Liversidge and Scaife, even if deemed proper, does not result in the claimed invention, which claims a "pharmaceutical composition comprising metaxalone in a micronized form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when orally administered to a patient on an empty stomach, wherein at least 99% of the metaxalone has a particle size not more than 10μm in diameter and wherein at least 63% of the metaxalone has a particle size more than 1.8μm in diameter."

Martin does not teach the claim features of claim 1. Martin is directed to increasing bioavailability of poorly soluble or water soluble drugs, and particularly griseofulvin. See Martin at col. 3, lines 14-17, and 55-56. Martin does not identify any specific particle sizes or range of particle sizes for griseofulvin, or any other drug. Martin teaches use of ultramicrocrystalline griseofulvin over that of micronized griseofulvin, but does not identify any specific sizes for either. The proposed combination of Martin and Scaife, even if deemed proper, does not result in the claimed invention, which claims a "pharmaceutical composition comprising metaxalone in a micronized form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when orally administered to a patient on an empty stomach, wherein at least 99% of the metaxalone has a particle size not more than 10μm in diameter and wherein at least 63% of the metaxalone has a particle size more than 1.8μm in diameter."

The secondary reference Scaife does not meet the deficiencies in the primary references. Scaife teaches a method for increasing the extent of absorption of a form of metaxalone by administering it with food. Scaife's teaching, however, results in a decrease in the rate of absorption.

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As shown in the present application, and as further supported by the concurrently filed Declaration of Nitin Bhalachandra Dharmadhikari (a co-inventor of the present invention):

> [T]he claimed invention provides the unexpected benefits of an increase in both the extent and rate of absorption of metaxalone when administered without to a patient on an empty stomach. The benefits of the present invention are indeed unexpected because the data in Scaife suggests that the extent of absorption and the rate of absorption are inversely correlated when one tries to increase bioavailability of a drug. *See* Table II b Col. 5 of Scaife. As previously noted in the Response mailed June 3, 2009, Table II b Column 5 of Scaife states that the Scaife composition when administered to a patient without food has a faster Tmax (Time to reach the peak plasma level of 3.32 hours) and lower AUC numbers (i.e., extent of absorption) than the same composition when administered to a patient with food (Tmax time is 4.29 hours). Thus, Scaife teaches that while the AUC numbers are greater when the Scaife composition is given to a patient with food than without food, it takes longer to reach peak levels (i.e., rate of absorption) when the Scaife composition is given to a patient with food than without food.
>
> Although Scaife (in column 6, lines 36-37 and lines 45-47) states that the composition has a higher rate and extent of absorption, such conclusion is incorrect in view of an increase in Tmax upon administration with food. Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (*See* Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, submitted in an Information Disclosure Statement filed on October 13, 2006).
>
> Generally, Tmax is related to the rate constant of absorption k_a by the equation:
>
> $$Tmax = \frac{2.303}{k_a - K} \log \frac{k_a}{K}$$
>
> K is the rate constant of elimination of drug from the body, and is unaffected by the presence of food. Therefore, changes in Tmax are related to changes in apparent rate constant of absorption.

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On the other hand Cmax is given by the equation:

$$Cmax = \frac{F X_0 e^{-KTmax}}{V}$$

where F is the extent of absorption, X_0 is the dose, V is the volume of distribution, and Tmax the time to peak plasma concentration. (*See* Milo Gibaldi et al., pg 37-38, Equations 1.106 and 1.110, submitted as Exhibit B of the Response dated July 2, 2007).

Therefore, Cmax is dependent on both extent (F) and rate of absorption, i.e., Tmax. An increase in Cmax without a decrease in Tmax may thus be only due to an increase in the extent of absorption, i.e., F. For further background generally regarding the rate and extent of absorption, see Bioavailability and Bioequivalence: General Concepts and Overview, by Prof Richard Bergstrom et al. of Indiana University, posted on the net at: http://medicine.iupui.edu/clinical/F813_spring2006/Q_ClinicalPKF813Lecture16A07March2006BioavailabilityandBioequivalencerevised.pdf, (submitted as Exhibit C of the Response dated July 2, 2007).

On the other hand, Table 8 of the present application shows that a micronized form of metaxalone exhibits both a decrease in Tmax (i.e., an increase in the rate of absorption) and an increase AUC numbers (i.e., an increase in the extent of absorption) over the Skelaxin composition (i.e., the Scaife composition) when those compositions are administered to patients without food. This is unexpected in view of the teachings of Scaife that increasing the extent of absorption comes by administering the Scaife composition with food also results in an increase in Tmax, i.e., a decrease in the rate of absorption. The Office Action does not rebut these arguments that the Applicants made previously.

[*See* ¶ 5 of the Dharmadhikari Declaration.]

The examiner in the present Office Action does not provide any basis to rebut the applicant's previous arguments that there was no reasonable expectation that both rate and the

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extent of absorption of metaxalone would be enhanced on an empty stomach by following the teachings laid down in Liversidge. It is reiterated that the obviousness test requires that a person of ordinary skill in the art should have a reasonable expectation of success. The Federal Circuit court in *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 997, 90 U.S.P.Q.2d 1947, 1951 (Fed. Cir. 2009) noted that "patents are not barred just because it was obvious 'to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *In re O'Farrell, 853 F.2d at 903*."

The Office Action ignores the above-identified inverse correlation taught in Scaife and incorrectly states (at p. 6 of the Office Action) that there is no evidence provided that shows that one of ordinary skill in the art would not expect both rate and extent of absorption or metaxalone to increase when provided to the same group of subjects, i.e., those without food.

The benefits of the present invention are indeed unexpected for the further reason that Liversidge teaches away from microsized drug particles in favor of nanosized drug particles, and for the further reason that Martin teaches away from microsized drug particles in favor of ultramicrocrystalline drug particles.

Additional unexpected results of the claimed invention are shown by the fact the claimed invention provided greater bioavailability when administered to patients without food than when administered to the patients with food. *See* Declaration of Nitin Bhalachandra Dharmadhikari at ¶¶ 6-10. This is indeed unpredictable because metaxalone is known to be a water insoluble drug with bioavailability problems. One of ordinary skill in the art at the time of invention would not be in a position to predict even with a reasonable expectation of success that the micronized form of metaxalone would provide a greater rate and extent of absorption compared to the composition of Scaife (i.e., commercialized as Skelaxin®) when **administered on an empty stomach.**

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Conclusion

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,

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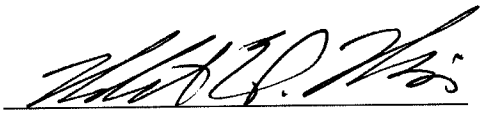
Date: May 6, 2010

By: 

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